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Procopiu

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(54) **PROCESS FOR PREPARING SALMETEROL**

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application No. PCT/GB01/02624 on Jun. 13, 2001,
now Pat. No. 6,911,560.

(30) **Foreign Application Priority Data**

Jun. 14, 2000 (GB) 0014546.6

(51) **Int. Cl.**
C07D 319/08 (2006.01)

(52) **U.S. Cl.** **549/365**

(58) **Field of Classification Search** 549/365
See application file for complete search history.

(56) **References Cited**

FOREIGN PATENT DOCUMENTS

EP	0422889	4/1991
EP	0460924	4/1991
GB	2140800	12/1984

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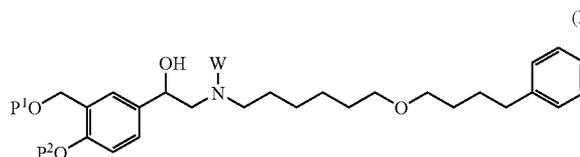
Hett et al., "Enantioselective synthesis of salmeterol via asymmetric
borane reduction," *Tetrahedron Letters* 35(50):9375-9378 (1994).

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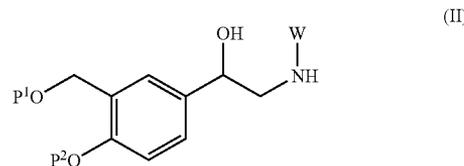
(57) **ABSTRACT**

A process for the preparation of a compound of formula (I)

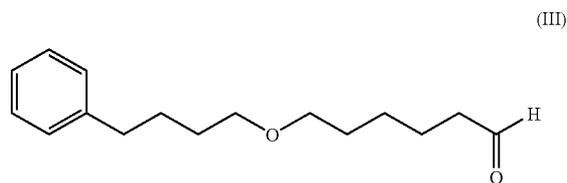


or a single enantiomer thereof, or a salt or a solvate thereof,
wherein W is a chiral auxiliary or hydrogen and P¹ and P²
are each independently selected from hydrogen or a protect-
ing group, which comprises:

a) treatment of a compound of formula (II),



or a salt or a solvate thereof, wherein W is a chiral
auxiliary and P¹ and P² are each independently chosen
from a protecting group, with a compound of formula
(III) to form a resulting product,



b) treating the resulting product with a reducing agent to
form the compound of formula (I), or a single enanti-
omer thereof, or a salt or a solvate thereof.

6 Claims, No Drawings

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PROCESS FOR PREPARING SALMETEROL

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation application of Ser. No. 10/297,130 filed Dec. 3, 2002, now U.S. Pat. No. 6,911,560, the application of which was filed under 35 U.S.C. § 371 as the United States National Phase Application of International Application No. PCT/GB01/02624 filed Jun. 13, 2001 claiming priority from UK patent application No. 0014546.6 filed Jun. 14, 2000.

This invention relates to a process for the preparation of salmeterol and to intermediates in the process.

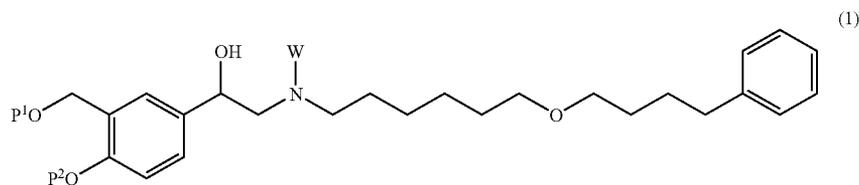
Processes for preparing salmeterol either as a racemate or in enantiomerically pure form have been described in GB 2140 800 and EP 0422 889.

EP 0460924 discloses the compound (R)-(-)-4-amino-3,5-dichloro- α -[[[6-[2-(2-pyridinyl)ethoxy]hexyl]amino]methyl]benzenemethanol and processes for its preparation employing chiral auxiliaries.

Methods of preparing a substantially pure single enantiomer often involve the resolution of diastereoisomers. However where one enantiomer is preferred this process is wasteful unless the unwanted enantiomer can be recycled. It is preferable to be able to efficiently synthesise directly one enantiomer in a substantially pure form.

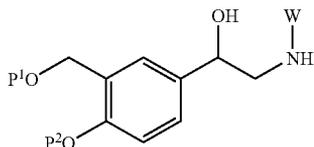
The present invention relates to a new process for the preparation of salmeterol especially as a single enantiomer, which may result in time and/or cost savings and the enantiomeric excess may be superior to that previously obtainable.

Accordingly, the present invention provides a process for the preparation of a compound of formula (I)



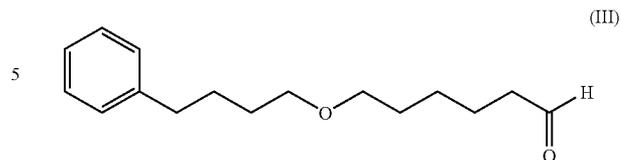
or a single enantiomer thereof, or a salt or a solvate thereof, wherein W is a chiral auxiliary or hydrogen and P¹ and P² are each independently selected from hydrogen or a protecting group, which comprises:

a) treatment of a compound of formula (II),



or a salt or a solvate thereof, wherein W is a chiral auxiliary and P¹ and P² are as defined above, with a compound of formula (III),

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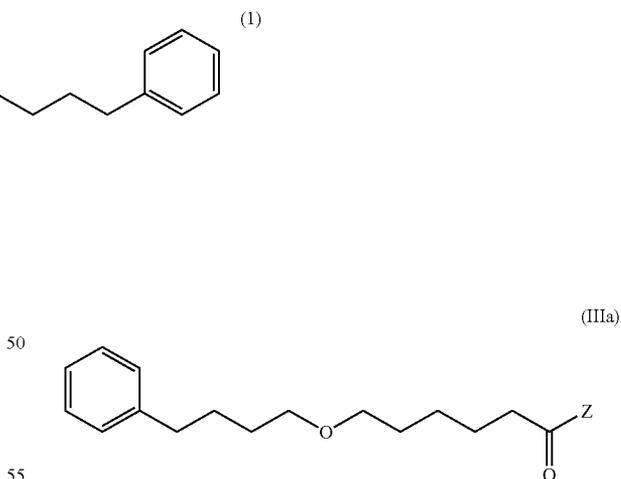


b) treatment of the resulting product with a reducing agent,

c) if required, deprotection to yield the compound of formula (I), or a salt or solvate thereof.

This process uses a commercially well established intermediate (referred to as compound of formula (V) below) known in the synthesis of salmeterol in a simple and robust process that may be used on a commercial scale the process uses relatively mild reagents with minimal toxicity that are readily available and inexpensive and does not require the use of sensitive or expensive catalysts that may be environmentally damaging especially when used on a large scale. Furthermore the yield of the process means the chiral synthesis of salmeterol using this process is now commercially viable.

Advantageously the process is very clean, avoiding the formation of undesirable biproducts, such as caused by esterification of the unprotected hydroxyl β to the nitrogen including the hydroxyl in the chiral auxiliary, which reduces the amount of purification necessary for the final product which may result in cost savings. Such esterification by-products have surprisingly been found to be a particular problem with use of analogous compounds of formula (III) represented by the formula (IIIa)



wherein Z represents halogen, hydroxyl or together with the carbonyl represents an activated ester. The problem is particularly evident wherein Z represents halogen.

Additionally since the process does not require the hydroxyl β to the nitrogen to be protected (e.g. with a protecting group as such, or else masked as a carbonyl), it avoids the unnecessary use of unpleasant reducing agents (e.g. diborane) at a late stage in the process and/or expensive catalysts or protecting reagents.

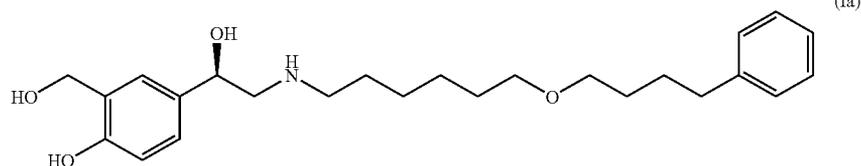
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Furthermore maintaining the presence of the chiral auxiliary in the compound of formula (II) during the coupling between the compound of formula (II) and the compound of formula (III) ensures that only the desired product is obtained because the chiral auxiliary acts as a protecting group in this reaction.

In one or more of these respects the process is advantageous over processes described in the prior art, such as EP 460924.

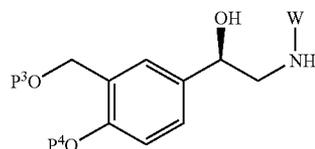
The process also provides an efficient way of producing a substantially pure single enantiomer of salmeterol.

Thus a suitable process for the preparation of the compound of formula (Ia)



(R-salmeterol) or a salt or a solvate thereof, comprises:

a) treatment of a compound of formula (II¹),



or a salt or a solvate thereof, wherein W is a chiral auxiliary and P³ and P⁴ independently represent a protecting group, with a compound of formula (III) as defined above

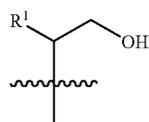
b) treatment of the resulting product with a reducing agent,

c) if required, deprotection to yield the compound of formula (Ia),

d) optional conversion to a corresponding salt or solvate thereof.

An analogous process may be used to prepare S-salmeterol by selecting a suitable chiral auxiliary.

Preferably W represents a chiral auxiliary, more preferably W represents a moiety of formula (Y)

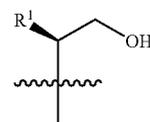


or a single enantiomer thereof, wherein R¹ represents C₁₋₆alkyl e.g. iso-propyl, iso-butyl or sec-butyl or optionally substituted phenyl or benzyl wherein the optional substitu-

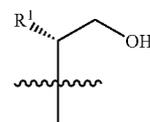
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tion is one or more independently selected from C₁₋₆alkyl, halogen, hydroxy, C₁₋₆alkoxy or nitro e.g. para-hydroxyphenyl.

More preferably W may represent Y¹

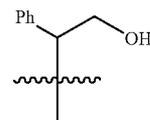


wherein R₁ is as defined above. Alternatively it represents a moiety of formula (Y²)

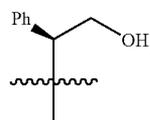


wherein R¹ is as defined above, especially a moiety of formula (Y²). Preferably R¹ represents phenyl optionally substituted as described above, iso-propyl or sec-butyl.

In an especially preferred aspect of the invention W represents a moiety of formula (Ya),



most preferably the moiety of formula (Ya¹),



and/or the moiety of formula (Ya²),

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extreme temperatures, for example -10 to 60°C ., especially 10 to 60°C ., for example ambient temperature, in an inert solvent such as dichloromethane (DCM) possibly in the presence of a water scavenger for example molecular sieves, magnesium sulphate or triethylorthoformate.

The protecting groups and/or the chiral auxiliary may be chosen so that they are removed during a step in the process rather than requiring a separate deprotection step. This may minimise the requirements for deprotection, at the end of the process, to yield compounds of formula (I). Preferably all deprotections will be effected when the chiral auxiliary is removed. Deprotection when used in this specification may refer to or include the removal of the chiral auxiliary.

Reduction with a hydride reducing agent can be performed in an inert aprotic solvent for example DCM or tetrahydrofuran in a nitrogen atmosphere typically at non-extreme temperatures, for example -10 to 60°C ., especially 10 to 60°C ., particularly ambient temperature.

Compounds of formula (III) can be prepared from oxidation of 6-(4-phenyloxy)hexyl bromide the preparation of which is described in DE 3414752.

Compounds of formula (II) defined above also form an aspect of the invention, in particular some non-limiting examples include:

1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-[(2-hydroxy-1-phenylethyl)amino]ethanol;

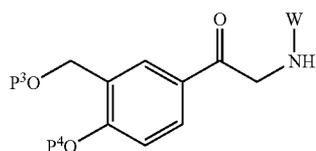
2-[[2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino]-3-methylpentan-1-ol;

2-[[2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino]-3-methylbutan-1-ol;

2-[[2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino]-3-phenylpropan-1-ol;

2[[2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino]-3-methylpentan-1-ol.

Also provided is a process for the preparation of compounds of formula (II) as defined above which comprises, treatment of a compound of formula (IV)



wherein W is a chiral auxiliary and p^3 and p^4 are defined above, with a reducing agent such as a hydride source e.g. sodium borohydride. Preferably this process takes place in the presence of an inert metal salt such as calcium chloride suitably at non-extreme temperatures e.g. below ambient, such as 0°C . This allows the desired stereochemistry to be introduced efficiently with good enantiomeric excess at an early stage in the synthesis, using inexpensive and relatively harmless reagents. Furthermore the enantiomeric excess may be increased by recrystallisation of the product of this process.

Compounds of formula (IV) are novel and also form an aspect of the invention; in particular some non-limiting examples include:

1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-[(2-hydroxy-1-phenylethyl)amino]ethanol;

1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-[[1-(hydroxymethyl)-2-methylbutyl]amino]ethanol;

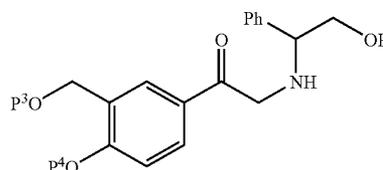
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1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-[[1-(hydroxymethyl)-2-methylpropyl]amino]ethanol;

2-[[1-(1-benzyl-2-hydroxyethyl)amino]-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol];

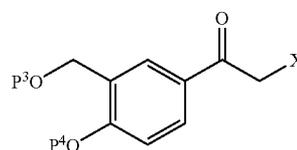
1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-[[1-(hydroxymethyl)-3-methylbutyl]amino]ethanol.

Compounds of Formula (IVa)



(IVa)

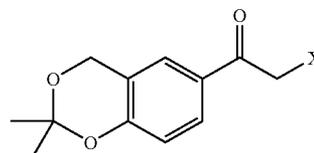
wherein P^3 and P^4 are as defined above, can be prepared from compounds of formula (V)



(V)

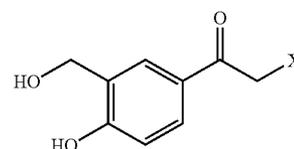
wherein X represents a leaving group e.g. halogen preferably bromine, and P^3 and P^4 are defined above, by treatment with (S)-phenylglycinol, in the presence of a non-nucleophilic base in an inert solvent at non-extreme temperatures e.g. 0 to 60°C ., e.g. room temperature. Preferably P^3 and P^4 together with the oxygens to which they are attached represent acetonide during this reaction.

Preferably compounds of formula (IV) may be prepared from compound of formula (Va)



(Va)

wherein X is a leaving group for example halogen such as chloro, bromo or iodo; or compounds of formula (IV) may be prepared from compounds of formula (Vb)



(Vb)

wherein X is a leaving group e.g. halogen.

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Other compounds of formula (IV) may be prepared by analogous processes.

Most preferably compounds of formula (IV) will be prepared from compounds of (Va). Compounds of formula (Va) can be prepared from treating 2-bromo-1-(4-hydroxy-3-hydroxymethyl-phenyl)ethanone, the preparation of which is described in GB 2140 800, with 2-methoxypropene in acetone in the presence of an acid for example p-toluenesulphonic acid in a nitrogen atmosphere.

Other compounds of formula (V) can be prepared by standard methods from 2-bromo-1-(4-hydroxy-3-hydroxymethyl-phenyl)ethanone.

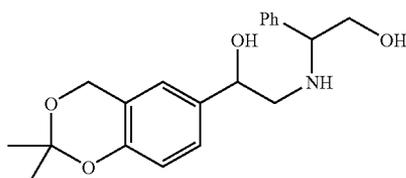
It will be clear to persons skilled in the art the enantiomeric excess obtained in the compound of formula (I) will depend on the enantiomeric excess of intermediate (II) which in turn is influenced by the enantiomeric excess of the chiral auxiliary. If desired, the above process may be adapted for preparation of racemic salmeterol using racemic intermediates.

Preferably, however, the process prepares one enantiomer of salmeterol suitably free of the other enantiomer e.g. in enantiomeric excess of greater than 90%, preferably greater than 95%, especially greater than 99%.

Intermediates should preferably be used in enantiomeric excess of 90%, preferably greater than 95%, especially greater than 99%.

Other aspects of this invention include the use of compounds of formula (II) and (IV) and (V) or deprotected derivatives thereof in the preparation of compounds of formula (I), salmeterol, single enantiomers thereof, or a salt or a solvate thereof.

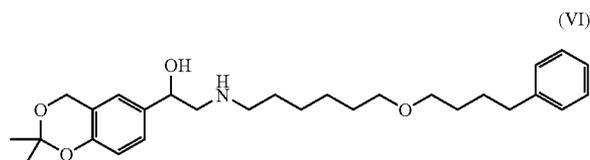
According to another aspect of the invention, is provided a compound of the formula (IIc),



or a single enantiomer thereof or a salt or a solvate thereof.

Advantageously compounds of formula (IIc) are crystalline which aids purification and are therefore preferred.

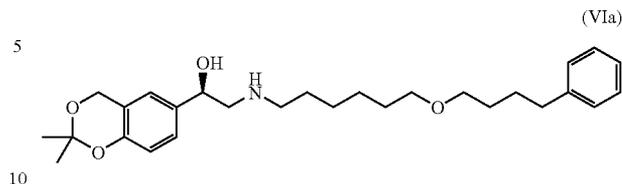
According to another aspect of the invention, is provided the intermediates of the general formula (VI),



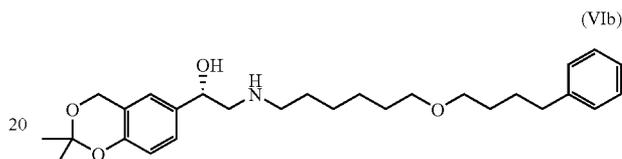
or a salt or solvate thereof;

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an intermediate of formula (VIa)

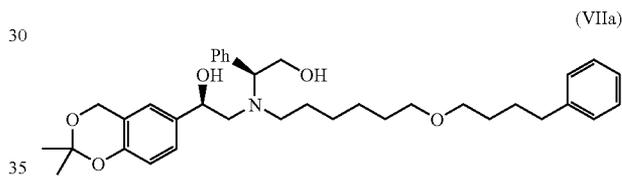


and/or a salt or a solvate thereof; and/or intermediate of formula (VIb)

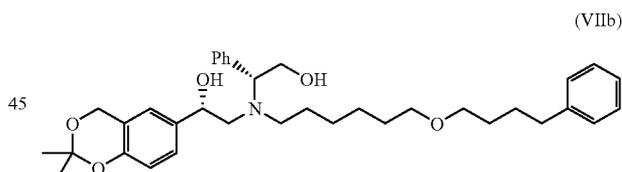


or a salt or a solvate thereof.

According to a further aspect of the invention, is provided an intermediate of formula (VIIa),



and/or a salt or a solvate thereof and an intermediate of formula (VIIb)



or a salt or solvate thereof.

A further aspect of the invention is use of compounds of formula (II) in the preparation of compounds of formula (I), and also the use of compounds of formula (IV) and (V) in the preparation of compounds of formula (II) or salts or solvates thereof.

EXAMPLES

LCMS was conducted on an ODS2 column (5 cmx4.6 mm) eluting with 0.05% HCO₂H (solvent A) and 0.05% HCO₂H in acetonitrile (solvent B), using the following elution gradient Omin 10% B, 0-12 min 90% B, 12-15 min 90% B, 15-17 min 10% B at a flow rate of 1 ml/min detecting at 230 nm. The mass spectra were recorded on a Fisons VG Platform spectrometer using electrospray positive mode (ES+ve).

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1-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-[[*(1S)*-2-hydroxy-1-phenylethyl]amino]ethanone

(*S*)-Phenylglycinol (28.9 g) was added in two portions to a solution of 2-bromo-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanone (40g) and *N,N*-di-iso-propylethylamine (48.9 ml) in THF (500 ml) under nitrogen. After 4h the resulting white precipitate was removed by filtration and the mother liquor concentrated in vacuo to give an orange oil. Acetonitrile (40 ml) was added and then removed in vacuo to give a light orange solid which was pulverised and triturated with cold acetonitrile (50 ml). The resulting solid was collected by filtration and washed with acetonitrile (2×30 ml) to give the title compound (38.5 g) as a white solid.

¹H NMR includes δ (CDCl₃, 300Mz): 1.47 (6H, s), 2.40 (1H, bs), 3.59 (1H, dd, J=11, 9 Hz), 3.70 (1H, dd, J=11, 4 Hz), 3.81 (1H, dd, J=9, 4 Hz), 3.88 (1H, d, J=18 Hz), 3.97 (1H, d, J=18 Hz), 4.77 (2H, s), 6.7-7.7 (8H, m).

(1*R*)-1-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-[[*(1S)*-2-hydroxy-1-phenylethyl]amino]ethanol

To a cooled mixture (internal temp. 2° C.) of 1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-[[*(1S)*-2-hydroxy-1-phenylethyl]amino]ethanone (44.9 g) in methanol (450 ml) under nitrogen was added CaCl₂·2H₂O (38.7 g) in one portion resulting in a slight exotherm (max temp ~12° C.). After the resulting clear solution had cooled to 0° C., sodium borohydride (10.5 g) was added in four portions over a 50 min period. After a further 2h at this temperature the volatile material was removed in vacuo resulting in a thick white slurry, to which ethyl acetate (500 ml) was added. The mixture was filtered through a short plug of Hyflo Supercel and the filtrate washed with water (150 ml), brine (150 ml), dried (Na₂SO₄) and concentrated in vacuo to give a thick orange oil. The oil was dissolved in acetonitrile (150 ml) and cooled to 5° C. for 18 h. The resulting crystals were filtered and washed with acetonitrile (3×30 ml) to give the title compound (23.9 g). The mother liquor from the filtration was concentrated in vacuo and taken up in acetonitrile (50 ml), cooled to 5° C. for 18 h to provide (after filtration and washing) a second crop of the title compound (3.4 g).

¹H NMR includes δ (CDCl₃, 300Mz): 1.43 (6H, s), 2.55 (1H, dd, J=12, 9 Hz), 2.65 (1H, dd, J=12, 4 Hz), 2.88 (1H, bs), 3.57 (1H, dd, J=11, 9 Hz), 3.67 (1H, dd, J=11, 4 Hz), 3.73 (1H, dd, J=9, 4 Hz), 3.54 (1H, dd, J=9, 3 Hz), 4.71 (2H, s), 6.64-7.30 (8H, m). LCMS RT=5.11 min, ES+ve 344 (MH⁺)⁺

[α]_D²⁰+43.1 (c 1.02 in CH₂Cl₂)

6-(4-Phenylbutoxy)hexanal

A mixture of DMSO (100 ml) and NaHCO₃ (14.1 g) was heated to 150° C. under nitrogen (the mixture had been thoroughly de-gassed prior to heating). 6-(4-Phenylbutoxy)hexyl bromide (10.0 g) was then added in one portion and the mixture was stirred at 150° C. for 5-6 min before it was cooled to 20° C. over a 10 min period. Diethyl ether (100 ml) was added, followed by water (100 ml). The layers were separated and the aqueous layer extracted with diethyl ether (200 ml). The combined organic layers were washed with water (2×100 ml), dried (MgSO₄) and concentrated in vacuo to give the title compound (8.4 g) which was used without further purification.

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LCMS RT=12.03 min, ES+ve 249 (MH⁺)⁺

(1*R*)-1-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-[[*(1S)*-2-hydroxy-1-phenylethyl][6-(4-phenylbutoxy)hexyl]amino]ethanol

To a cloudy mixture of (1*R*)-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-[[*(1S)*-2-hydroxy-1-phenylethyl]amino]ethanol (500 mg) and crude 6-(4-phenylbutoxy)hexanal (400 mg) in CH₂Cl₂ (3 ml) under nitrogen was added sodium triacetoxyborohydride (433 mg) in one portion. A gelatinous mixture formed initially which thinned over a 15 min period. The resulting light yellow solution was stirred for 18 h before it was partitioned between ethyl acetate (10 ml) and saturated aqueous NaHCO₃ (30 ml). The aqueous layer was extracted with ethyl acetate (3×20 ml) and the combined organic layers were dried (MgSO₄) and concentrated in vacuo to give the title compound (725 mg).

¹H NMR includes δ (CDCl₃, 400Mz): 1.18-1.38 (5H, m), 1.53 (6H, s), 1.40-1.71 (9H, m), 2.33-2.41 (1H, m), 2.59-2.70 (4H, m), 2.82 (1H, dd, J=13, 5 Hz), 3.37 (2H, t, J=7 Hz), 3.41 (2H, t, J=7 Hz), 3.80 (1H, dd, J=9, 4 Hz), 3.90-4.00 (2H, m), 4.60 (1H, dd, J=9, 4 Hz), 4.83 (2H, s), 6.79 (1H, d, J=8 Hz), 6.96 (1H, d, J=2 Hz), 7.09 (1H, dd, J=8, 2 Hz), 7.15-7.2 (3H, m), 7.21-7.37 (7H, m)

LCMS RT=7.92 min, ES+ve 576 (MH⁺)⁺

[α]_D²⁰-9.0 (c 1.6 in CHCl₃)

(1*R*)-(-)-2-Hydroxymethyl-4-{1-hydroxy-2-[[6-(4-phenylbutoxy)hexyl]amino]ethyl]phenol

A solution of (1*R*)-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-[[*(1S)*-2-hydroxy-1-phenylethyl][6-(4-phenylbutoxy)hexyl]amino]ethanol (110 mg), in ethanol (75 ml), was hydrogenated over Pearlman's catalyst [Pd(OH)₂, 60% H₂O, 55 mg] for 18 h. The catalyst was removed by filtration and the residue washed with methanol. The combined filtrate and washings were concentrated and then applied to a 10 g SCX ion exchange cartridge. The cartridge was eluted with methanol (4 column volumes) and then with 10% aqueous 880 NH₃ in methanol (3 column volumes). The ammoniacal eluent was concentrated under reduced pressure to give the title compound (69 mg) as a colourless oil.

LCMS RT=6.27 min, ES+ve 416 (MH⁺)⁺.

[α]_D²⁰-18.5 (c 0.81 in methanol)

Chiral HPLC on chiralcel column indicated only the presence of the R enantiomer RT=9.704 min

(1*R*)-(-)-2-Hydroxymethyl-4-{1-hydroxy-2-[[6-(4-phenylbutoxy)hexyl]amino]ethyl]phenol, 1-hydroxy-2-naphthalenecarboxylic acid salt

A solution of (1*R*)-(-)-2-hydroxymethyl-4-{1-hydroxy-2-[[6-(4-phenylbutoxy)hexyl]amino]ethyl]phenol (53 mg) in methanol (2 ml) was treated with 1-hydroxy-2-naphthoic acid (24 mg). The solution was evaporated to dryness to give the title compound as a solid (77 mg)

Chiral HPLC conducted on a 25 cm×0.46 cm Sumichiral OA4100 column, eluting with hexane-dichloromethane-ethanol-trifluoroacetic acid [240:130:30:1] at a flow rate of 1 ml/min indicated the presence of the R enantiomer (98.5%) RT=18.787 min and the S enantiomer (1.5%) RT=16.417 min. The ee =97%.

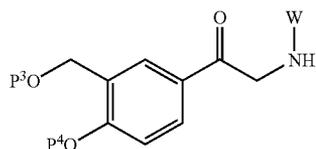
Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise',

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and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

The invention claimed is:

1. A compound of formula (IV)



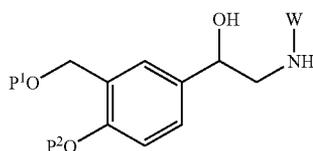
(IV)

wherein W is a chiral auxiliary and P³ and P⁴ each independently represent a protecting group, or a salt or solvate thereof.

2. A compound of formula (IV) according to claim 1, wherein said compound is selected from the group consisting of:

1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-[(2-hydroxy-1-phenylethyl)amino]ethanone;
 1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-[[1-(hydroxymethyl)-2-methylbutyl]amino]ethanone;
 1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-[[1-(hydroxymethyl)-2-methylpropyl]amino]ethanone;
 2-[(1-benzyl-2-hydroxyethyl)amino]-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanone; and
 1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-[[1-(hydroxymethyl)-3-methylbutyl]amino]ethanone.

3. A process for the preparation of a compound of formula (II):

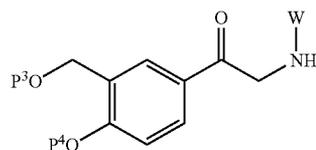


(II)

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or a salt or a solvate thereof, wherein W is a chiral auxiliary and P¹ and P² are each independently chosen from a protecting group, wherein said process comprises treating a compound of the formula (IV)

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(IV)

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wherein W is a chiral auxiliary and P³ and P⁴ are each independently chosen a protecting group, with a reducing agent to form the compound of formula (II).

4. A process according to claim 3 wherein the reducing agent is a hydride source.

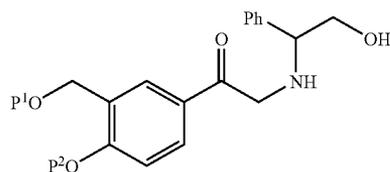
5. A process according to claim 3 wherein the reduction is performed in the presence of an inert metal salt.

6. A compound of formula (IVa)

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(IVa)

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or a single enantiomer thereof, or a salt or a solvate thereof wherein P¹ and P² are each independently chosen from hydrogen or a protecting group.

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